ORIGINAL ARTICLE

Incidence and outcome of critically ill patients with COVID-19 and Acute kidney Injury in tertiary care centre of north-west India

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ABSTRACT

Background: The clinical manifestations of the COVID-19 range from asymptomatic to a fulminant and rapidly fatal infection. Studies show that the incidence of acute kidney injury (AKI) in COVID-19 patients vary widely from 0.5 to 80%.

Objective:This study was conducted to study the incidence and outcome of critically ill patients having COVID-19 infection along with AKI at a tertiary care center.

Design:A prospective cohort study done over a period of one month.

Setting: In this study, all adult (⩾ 18 years) patients admitted in Intensive Care Unit (ICU) and have tested positive for COVID-19 via RT-PCR test were included. All patients found to have AKI were assessed for comorbidities like diabetes, hypertension, Coronary artery disease, Stroke etc. Patients were followed up during the hospital stay.

Results: Incidence of AKI among COVID-19 patients was found to be 32.3%. There was significant ($p<0.05$) association of incidence of AKI with cough, fever, high total leucocyte count, use of face mask, use of high flow mask, diabetes and coronary artery disease (CAD). Cough ($p=0.01$), use of face mask ($p=0.006$), invasive mechanical ventilation ($p=0.0001$) and hypertension ($p=0.03$) were significantly associated with mortality among these patients. Mortality was highest among patients of AKI stage III (95.7%).

Conclusion: Incidence of acute kidney injury in critically ill patients with COVID-19 hospitalized in a tertiary care centre in western part of India was high. AKI during hospitalization was associated with an increased risk of in-hospital death.

Keywords: COVID-19, Acute Kidney Injury, Critically ill

INTRODUCTION

In December 2019, a series of cases of acute respiratory illness occurred in Wuhan, Hubei Province, China. This disease was identified as COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. On March 11, 2020, the World Health Organization announced that the COVID-19 virus was officially a pandemic after it spread to more than 114 countries in just 3 months. More than 16 months after the first reported case, the virus is still spreading at a rapid rate with more than 100 million affected and more than 3 million dead. As India is struggled with a devastating second wave, the health care resources have been stretched to the limit. Physician, including nephrologist have had to rapidly adapt their practice to handle the large number of cases presenting to them. The clinical manifestations of the Covid-19 range from asymptomatic to a fulminant and rapidly fatal infection. The primary target of coronavirus disease is, the lungs but high incidences of acute kidney injury (AKI) have been reported. Initially, an incidence of AKI in hospitalized COVID-19 patients has been reported to be 34%[1]. In critically ill patients the incidence increased to 78%[1]. But, further studies found that the incidence of AKI in COVID-19 patients to vary widely from 0.5% to 80%[2]. This study was conducted to describe the clinical characteristics and risk factors for AKI and death among critically ill patients of COVID-19 who were treated in the ICU of our hospital.

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MATERIALS AND METHODS

All patients presenting to the Intensive Care Unit (ICU) who tested positive for COVID-19 via RT-PCR were approached for inclusion into the study. Patient on immunosuppressive agents, with pre-existing chronic kidney disease and renal transplant recipients were excluded. After obtaining informed consent, a clinical profile was collected in a standard proforma. All patients found to have acute kidney injury were assessed for comorbidities like diabetes, hypertension, Coronary artery disease (CAD), stroke etc. Patients were followed up during the hospital stay and were assessed for need of oxygen (via face mask, high flow nasal cannula or high flow face mask), non-invasive or invasive mechanical ventilation. Proteinuria and hematuria were assessed using a dipstick. Need for vasopressors/ inotropes was assessed. Stage of AKI was calculated using KDIGO guidelines. Renal replacement therapy in the form of hemodialysis or peritoneal dialysis was used according to standard practice guidelines.

Definitions

AKI was identified according to the Guidelines of Kidney Disease: Improving Global Outcomes (KDIGO)[3]. It is defined as any of the following: an increase in Serum Creatinine of ⩾ 0.3 mg/dL within 48 hours; an increase in Serum Creatinine of ⩾ 1.5 times the baseline, which is known or presumed to have occurred within the past 7 days; or urine volume < 0.5 mL/kg/hr for 6 hours.

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

RESULTS

The incidence of AKI was found to be 32.3%. Stage III AKI was among more than one third of patients (44.2%) followed by Stage I (28.8%) and Stage II (26.9%)Figure 1. About one third of patients were >60 years (34.2%). More than half of the patients were males (61.5%). The incidence of AKI was highest among patients of age >60 years (56.4%) and was lowest in <30 years (5%). The incidence of AKI was 24.54 times significantly higher among patients of age >60 years than <30 years (OR=24.54, 95%=3.06-196.50, p=0.003). The incidence of AKI was higher among males (36.4%) than females (25.8%), however, the association was statistically insignificant (p>0.05). Oxygen requirement was the most common (92.5%) and dyspnoea was the second most common factor (73.3%). CVA was the least common factor (5.6%). The incidence of AKI was 6.42 times significantly higher among whom dyspnoea was present than absent (OR=6.42, 95%CI=2.15-19.16, p=0.0001). There was significant (p<0.05) association of incidence of AKI with cough, fever, face mask, high flow mask, diabetes and CAD (Table 1). The incidence of AKI was 5.44 times significantly higher among whom TLC (Total Leukocyte Count) was abnormal than normal (OR=5.44, 95%CI= 2.00-14.82, p=0.0001). The factors found to be significant in univariate analysis were entered in the multivariate analysis. The multivariate analysis showed that the incidence of AKI was 12.44 times

significantly higher among patients of age >60 years than <30 years (Adjusted OR=12.44, 95%CI=1.42-127.76, p=0.03) when adjusted for dyspnoea and high flow mask. Dyspnoea (p=0.01) and high flow mask (p=0.0001) was also significantly associated with the incidence of AKI in multivariate model. Cough (p=0.01), face mask (p=0.006), invasive mechanical ventilation (p=0.0001) and hypertension (p=0.03) were significantly associated with mortality (Table 2). Mortality was higher among patients of AKI stage III (95.7%) than stage I (80%) and stage II (42.9%)Figure 2. The mortality was 82% significantly lower among patients of stage II than stage I (OR=0.18, 95%CI=0.03-0.97, p=0.04). Among the patients who developed AKI, we found the incidence of 1+, 2+, 3+ proteinuria to be 40%, 38% and 5.8% respectively. 15.4% of the patients had no proteinuria. Interestingly no patient in our study had 4+ proteinuria on dipstick examination. Concurrent haematuria of 1+ and 2+ was seen in 46.2% and 1.9% of the patients, respectively.

DISCUSSION

In this prospective cohort study conducted in Jaipur, Rajasthan, we observed an incidence of 32.3% of acute kidney injury in critically ill hospitalized patients with COVID-19. More than one third of these patients developed severe AKI, Stage III AKI. In our study, 14.28% of patients required renal replacement therapy.

The incidence of AKI reported in various studies varies from 0.5 to 80 percent[2]. In a meta-analysis[4] of approximately 13,000 mostly hospitalized patients, the incidence of AKI was 17 percent. Approximately 5 percent of patients required kidney replacement therapy (KRT) in this meta-analysis. The incidence of AKI seems to vary according to the number of critically ill patients included in the study. The high incidence of AKI in our study may be explained by the fact that we only included critically ill patients. The same may be the reason for higher number of patients requiring renal replacement therapy.

The incidence of AKI in critically ill patients, in pre COVID era has been found to be 39.3% in developed countries and 35.1% in the developing countries[5]. This is strikingly close to the incidence of AKI found in our study. The incidence of AKI was higher among the 2600 patients who had COVID-19 compared with over 19,500 patients who were hospitalized for other reasons (31 versus 18 percent)[6]. This higher incidence of AKI could not be explained by differences in the traditional risk factors for AKI between the groups. COVID-19 remained associated with a higher rate of AKI despite controlling for demographic variables, comorbidities, frequency of hypotension, selected laboratory results (eg, complete blood count, baseline eGFR), and use of nephrotoxic medications, vasopressors, or mechanical ventilation. Whether AKI in COVID-19 patients portents worse mortality outcomes than non-covid patients requires further study.

The etiology of AKI in critically ill patients with COVID-19 appears to be multifactorial. In AKI-EPI study done in pre-covid era, etiology of AKI in descending order was as follows: sepsis, hypovolemia, drug related, cardiogenic shock, hepatorenal syndrome, and obstructive uropathy[7].These are potential etiologies, even in critically ill patients of COVID-19 but whether SARS-CoV-2 causes a direct kidney infection remains controversial[8].The role of "cytokine storm" and the high incidence of thrombosis in patients of COVID-19 remain understudied causes of AKI in this Cohort[9,10].

A high incidence of AKI was seen in patients with respiratory failure. There was significant ($p<0.05$) association of incidence of AKI with oxygen requirement with a face mask or a high flow mask. Incidence of AKI was also higher among patients who required Non Invasive and Invasive mechanical ventilation, but the incidence was not found to be statistically significant.

In other studies, the incidence of AKI was higher in patients on high oxygen support[11].

Monitoring kidney function must therefore be emphasized even in patients with mild respiratory symptoms, and altered kidney function should be given particular attention after admission in clinical practice. Early detection and treatment of renal abnormalities, including adequate hemodynamic support and avoidance of nephrotoxic drugs, may help to improve the vital prognosis of COVID-19.

CT severity scores and markers of inflammation, such as C-reactive protein and ferritin, appeared to be

Table 1: Distribution of various factors and its association with incidence of AKI

Factors	No. (n=161)		With AKI		Without AKI		OR (95% CI)	P-value
	No.	%	No.	%	No.	%		
Dyspnea	118	73.3	48	40.3	70	59.7	6.42 (2.15-19.16)	0.0001*
Cough	72	44.7	15	20.8	57	79.2	0.37 (0.18-0.75)	0.005*
Fever	92	57.1	23	25	69	75	0.46 (0.23-0.90)	0.02*
Oxygen requirement	149	92.5	50	33.6	99	64.4	2.52 (0.53-11.96)	0.22
Nasal prongs	20	12.4	7	35.0	13	65.0	1.14 (0.42-3.07)	0.78
Face mask	28	17.4	1	3.6	27	96.4	0.06 (0.01-0.45)	0.0001*
High flow mask	22	13.7	14	63.6	8	36.4	4.65 (1.80-11.97)	0.001*
Non-invasive mechanical ventilation	52	32.3	18	34.6	34	65.4	1.16 (0.58-2.35)	0.66
Invasive mechanical ventilation	46	28.6	19	41.3	27	58.7	1.74 (0.85-3.56)	0.12
Diabetes	62	38.5	30	48.4	32	51.6	3.28 (1.65-6.52)	0.001*
Hypertension	63	39.1	26	41.3	37	58.7	1.94 (0.99-3.81)	0.06
CAD	17	10.6	10	58.8	7	41.2	3.46 (1.23-9.72)	0.01*
CVA	9	5.6	3	33.3	6	66.7	1.05 (0.25-4.37)	0.94
Need of vasopressors	48	29.8	19	39.6	29	60.4	1.58 (0.78-3.21)	0.19

OR-Odds ratio, CI-Confidence interval,*Significant

Table-2: Distribution of various factors and its association with mortality among critically ill patients.

Factors	No. of patients	Expired		Alive		OR (95%CI)	p-value
		No.	%	No.	%		
Dyspnea	118	61	51.7	57	48.3	1.63 (0.80-3.32)	0.17
Cough	72	27	37.5	45	62.5	0.44 (0.23-0.84)	0.01*
Fever	92	42	45.7	50	54.3	0.77 (0.41-1.43)	0.41
Oxygen requirement	149	73	49.0	76	51.0	1.34 (0.40-4.42)	0.62
Nasal Prongs	20	7	35.0	13	65.0	0.53 (0.20-1.40)	0.19
Face Mask	28	7	25.0	21	75.0	0.29 (0.11-0.73)	0.006*
High flow mask	22	10	45.5	12	54.5	0.87 (0.35-2.14)	0.76
Non-invasive Mechanical	52	21	40.4	31	59.6	0.61 (0.31-1.20)	0.15

Ventilation							
Invasive Mechanical Ventilation	46	38	82.6	8	17.4	8.90 (3.79-20.91)	0.0001*
Diabetes	62	36	58.1	26	41.9	1.87 (0.98-3.57)	0.06
Hypertension	63	37	58.7	26	41.3	1.97 (1.04-3.76)	0.03*
CAD (Coronary Artery Disease)	17	10	58.8	7	41.2	1.59 (0.57-4.42)	0.36
CVA (Cerebrovascular Accident)	9	5	55.6	4	44.4	1.35 (0.35-5.23)	0.66
Need for Vasopressors	48	25	52.1	23	47.9	1.23 (0.62-2.42)	0.54
Renal Replacement Therapy	23	21	91.3	2	8.7	14.92 (3.36-66.17)	0.0001*
Haemodialysis	11	9	81.8	2	18.2	5.28 (1.10-25.27)	0.02*
Peritoneal dialysis	14	13	92.9	1	7.1	16.40 (2.09-128.65)	0.001*
AKI	52	40	76.9	12	23.1	6.22 (2.92-13.26)	0.0001*

OR-Odds ratio, CI-Confidence interval, *Significant

higher among patients who had AKI compared with those who did not have AKI. However, the comparison between groups controlling for these inflammatory markers was not possible because the tests were not available for all the patients. A higher CT severity and marker of inflammation in those with AKI may be a pointer to a more severe disease, which may be the cause or effect or both in patients of COVID-19.

In our study, there was significant ($p<0.05$) association of incidence of AKI with older age, history of diabetes and CAD. There was a higher incidence of AKI among those with hypertension and history of CVA, but the incidence were not found to be statistically significant. Similarly, incidence of AKI was higher in those patients who required vasopressor support, but the incidence did not reach statistical significance. These are considered to be traditional risk factors for AKI. Patients with these comorbidities continue to be at risk for AKI, even among the patients of COVID-19 and frequent monitoring of renal functions of these patients may be warranted.

In our study, AKI was found to be significantly associated with mortality. Mortality was higher among patients of AKI stage III (95.7%) than stage I (80%) and stage II (42.9%). There was significant ($p<0.05$) association of mortality with requirement of renal replacement therapy. AKI has been found to be a risk factor for mortality in various studies of both COVID and non-COVID patients[11,12]. Whether AKI in COVID-19 patients portents worse mortality outcomes than non-COVID patients requires further study.

Among the patients who developed AKI, we found the incidence of 1+, 2+. 3+ proteinuria to be 40%, 38% and 5.8% respectively. 15.4 % of the patients had no proteinuria. Interestingly, no patient in our study had 4+ proteinuria on dipstick examination. Concurrent hematuria of 1+ and 2+ was seen in 46.2% and 1.9% respectively.

In most studies, where kidney biopsy was done in patients of COVID-19, the predominant kidney pathological finding was Acute Tubular Necrosis (ATN), but glomerular lesions have been reported in a minority of patients[13-17]. These findings explain the urinalysis findings in our patients. A renal biopsy could not be carried out in patients in our centre due to resource limitations, and the fact that all patients enrolled in the study were critically ill and many were haemodynamically unstable.

Even though this study included a substantial number of patients from a tertiary care hospital, it has several limitations. First, a baseline serum creatinine was not available for all patients, which may have led to an underestimation/overestimation of AKI or erroneous associations. Second, clinical data of patients after discharge were lacking, so we could not assess COVID-19 effects on long-term outcomes. The precise impact of COVID-19 on kidney structure and function and the incidence of chronic kidney disease in these patients require further investigation.

Our study represents the reality of public hospitals in our country. The findings described here, can help, not only in planning of future studies but also in

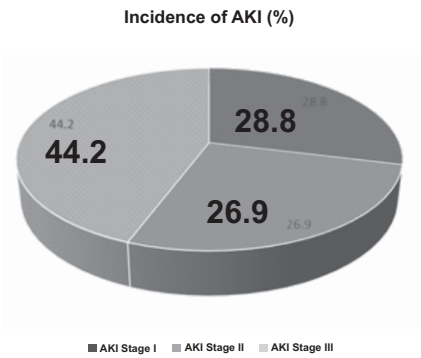

Figure 1: Incidence of AKI in COVID-19 patients according to AKI stages.

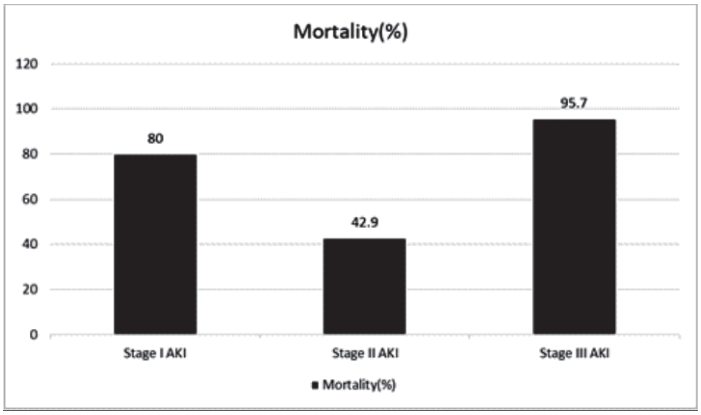

Figure 2: Mortality according to stages of AKI in COVID-19 patients

future planning of ICU care for critically ill patients of COVID-19. A high number of critically ill patients required renal replacement therapy and provisions for the same are an essential part of care for critically ill patients. The facility for the same is lacking in large parts of the country, and requires urgent attention.

In conclusion, the incidence of acute kidney injury in critically ill patients with COVID-19 hospitalized in Jaipur, was high. AKI during hospitalization was associated with an increased risk of in-hospital death. Clinicians should increase their awareness of kidney disease in hospitalized patients with COVID-19. Early detection and effective intervention of kidney involvement may help to reduce deaths of patients with COVID-19.

REFERENCES

1. Argenziano MG, Bruce SL, Slater CL. et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ 2020; 369:m1996.
2. Jia H. Ng, Vanesa Bijol, Matthew A. Sparks et al. Pathophysiology and pathology of acute kidney injury in patients with COVID-19. Advances in Chronic Kidney Disease 2020; 27(5):365-376.
3. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2(1):1–138.
4. Juarez SY, Qian L, King KL et al. Outcomes for Patients With COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis. Kidney Int Rep. 2020;5(8):1149. Epub 2020 Jun 25
5. Melo FAF, Macedo E, Fonseca Bezerra AC et al. A systematic review and meta-analysis of acute kidney injury in the intensive care units of developed and developing countries. PLoS One. 2020 Jan 17;15(1):e0226325.
6. Moledina DG, Simonov M, Yamamoto Y et al. The Association of COVID-19 With Acute Kidney Injury Independent of Severity of Illness: A Multicenter Cohort Study. Am J Kidney Dis. 2021;77(4):490. Epub 2021 Jan 8.
7. Hoste EA, Bagshaw SM, Bellomo R et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015 Aug;41(8):1411-23.
8. Lite C, Ahmed SSSJ, Juliet M et al.SARS-CoV-2/human interactome reveals ACE2 locus crosstalk with the immune regulatory network in the host. Pathog Dis. 2021;79(2)
9. Minami, T., Iwata, Y. & Wada, T. Renal complications in coronavirus disease 2019: a systematic review. InflammRegener 40, 31 (2020).
10. Ahmadian E, HosseiniyanKhatibi SM, RaziSoofiyani S et al. Covid-19 and kidney injury: Pathophysiology and molecular mechanisms. Rev Med Virol. 2021 May;31(3):e2176.
11. Bowe B, Cai M, Xie Y et al. Acute Kidney Injury in a National Cohort of Hospitalized US Veterans with COVID-19.Clin J Am SocNephrol. 2020;16(1):14. Epub 2020 Nov 16.
12. Hirsch JS, Ng JH, Ross DW et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209-218. Epub 2020 May 16.
13. Kudose S, Batal I, Santoriello D et al.Kidney Biopsy Findings in Patients with COVID-19. J Am SocNephrol. 2020;31(9):1959. Epub 2020 Jul 17.

14. Golmai P, Larsen CP, DeVita MV et al. Histopathologic and Ultrastructural Findings in Postmortem Kidney Biopsy Material in 12 Patients with AKI and COVID-19. J Am SocNephrol. 2020;31(9):1944. Epub 2020 Jul 16.
15. Werion A, Belkhir L, Perrot M et al. SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule. Kidney Int. 2020;98(5):1296. Epub 2020 Aug 10.
16. Akilesh S, Nast CC, Yamashita M et al. MulticenterClinicopathologic Correlation of Kidney Biopsies Performed in COVID-19 Patients Presenting With Acute Kidney Injury or Proteinuria. Am J Kidney Dis. 2021;77(1):82. Epub 2020 Oct 10.
17. Farkash EA, Wilson AM, Jentzen JM. Ultrastructural Evidence for Direct Renal Infection with SARS-CoV-2. Am SocNephrol. 2020;31(8):1683. Epub 2020 May 5.